IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIODELIVERY SCIENCES INTERNATIONAL, INC. and ARIUS TWO, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 18-1395 (CFC) (CJB)
ALVOGEN PB RESEARCH & DEVELOPMENT LLC, ALVOGEN MALTA OPERATIONS LTD., ALVOGEN PINE BROOK LLC, ALVOGEN, INC., and ALVOGEN GROUP, INC.,	)	
Defendants.	)	

ALVOGEN'S OPENING POST-TRIAL BRIEF

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Plaintiffs (collectively, "BDSI") brought this suit against Defendants (collectively, "Alvogen") (D.I. 1)[1] alleging infringement of U.S. Patent Nos. 8,147,866 ("the '866 patent") (JTX-001); 9,655,843 ("the '843 patent") (JTX-002); and 9,901,539 ("the '539 patent") (JTX-003) ("the patents-in-suit").

The Court held a three-day bench trial, addressing the validity of claims 3, 4, 5, and 10 of the '866 patent; claims 8, 9, and 20 of the '843 patent; and claims 9 and 20 of the '539 patent ("the asserted claims").

Pursuant to the Court's Order (D.I. 251), Alvogen submits this brief and findings of fact that the asserted claims are invalid as anticipated by or obvious in view of the prior art.

I. INTRODUCTION

The patents-in-suit claim a bioerodable mucoadhesive ("BEMA") device for transmucosal delivery of buprenorphine. BDSI did not invent these devices—Tapolsky did. BDSI licensed Tapolsky's patents, which it used to protect Belbuca® until Tapolsky's patents expired in 2020. The public should be free now to practice Tapolsky's BEMA devices.

In an effort to "evergreen" Tapolsky, however, in 2006 BDSI claimed a "new" treatment utilizing buprenorphine in Tapolsky's BEMA devices. There was nothing inventive about this "new" treatment. POSAs knew buprenorphine to be a

[1] Citations to "D.I. _" are to C.A. No. 1:18-cv-01395-CFC-CJB.

safe and effective drug for treating pain. At most, providing buprenorphine in Tapolsky's BEMA devices was a matter of routine skill. The Court should not permit BDSI to extend the Belbuca® patent monopoly and preclude generic competition for another twelve years to 2032 because BDSI substituted one opioid disclosed in Tapolsky (butorphanol) for another (buprenorphine).

Alvogen's opening statement presented the Court with two binary questions to be resolved through the trial. (Tr. at 41:19-25.)[2] The trial evidence resoundingly answers both and establishes that it was obvious to (1) utilize buprenorphine in Tapolsky's BEMA platform, and (2) buffer Tapolsky's polymeric diffusion environment to a pH that is optimal for buprenorphine delivery.

Alvogen's expert, Dr. Bozena Michniak-Kohn, testified that Bullingham, Tapolsky, Moro and numerous other prior art would have motivated a POSA to utilize buprenorphine in a BEMA device with a reasonable expectation of success. BDSI's experts never attempted to rebut this conclusion. The evidence is clear and convincing.

Nor does the prior art teach away from the claimed pH range, as BDSI argued in its opening. Every single prior art reference in evidence teaches an acidic pH environment that dissolved and ionized buprenorphine. Todd provides a pH of 4.5-5.5, and Suboxone® a pH of 3.5, in order to fully dissolve and ionize

[2] "Tr." refers to citations to the trial transcript.

buprenorphine. Cassidy teaches an exponential increase in buprenorphine solubility at these acidic pH values. Todd and Suboxone® teach that the oral mucosa absorbs ionized buprenorphine at these acidic pH values. A POSA would have been motivated to buffer Tapolsky's drug layer to an optimal pH of 4-6 to optimize buprenorphine delivery with a reasonable expectation of success.

In its opening, BDSI argued that saliva was the "enemy" of Belbuca®. As Dr. Michniak-Kohn explained, however, saliva buffered to acidic pH is what dissolves and ionizes the buprenorphine, causing it to leave the device and permeate the mucosa. At trial, BDSI proffered Dr. Robert Williams who opined that unionized drugs generally absorb better than ionized drugs. However, Dr. Williams conceded that buprenorphine is an exception to this general rule. He also conceded that buprenorphine (1) dissolves in saliva only when it is buffered to acidic pH values, (2) is fully ionized at these acidic pH values, and (3) permeates the mucosa in the dissolved and ionized state.

BDSI argued at the United States Patent and Trademark Office ("PTO")—and in its opening—that dissolving buprenorphine in saliva was not a concern because buprenorphine is soluble in the polymeric casting solution before the water is removed during manufacturing and the film is dried. Dr. Williams conceded, however, that buprenorphine, which is solid in the final dosage form, must nonetheless dissolve and ionize in the saliva in order to leave the device and

permeate the oral mucosa. Buprenorphine can only do so when in saliva buffered to acidic pH values. Furthermore, a POSA would have expected buprenorphine to dissolve from the device more rapidly and completely in saliva buffered to acidic pH values in view of the exponential increase in solubility shown by Cassidy at acidic pH values—a scientific fact admitted by BDSI's own formulators in documents it submitted to FDA. Again, the evidence is clear and convincing.

Unlike the record before the PTO, the trial record before the Court provides correct scientific facts and data that the PTO did not have. The evidence at trial proves that BDSI materially misrepresented the prior art Tapolsky, Suboxone®, Vasisht I, and other references and even its own claimed "invention." At trial, all experts agreed that Tapolsky disclosed opioid delivery through a BEMA device, and that Suboxone® includes buffers and has a pH of 3.5, but as to both BDSI falsely argued the opposite to the PTO in order to obtain its patents. In addition, the PTO withdrew its rejection of then-pending claims only after BDSI submitted the Finn and Vasisht declarations, which unquestionably and repeatedly make materially false arguments and present materially false data.

The PTO conducts *ex parte* examinations. Examiners do not have the benefit of an adversarial process, which is why applicants owe a duty of candor and must submit declarations under penalty of perjury. This Court knows what the PTO did not—the truth. The PTO was correct in its initial assessment to reject the

asserted claims, and, given the scientifically accurate and complete trial record here, this Court should do the same. BDSI evergreened obvious variants of Tapolsky only through a serial campaign of deception. The Court should strike down BDSI's patents as invalid.

II. BACKGROUND

A. Belbuca®

BDSI is the holder of approved New Drug Application ("NDA") No. 20-7932 for Belbuca®, which is multi-layered film applied to the user's cheek (buccal surface) and is indicated for the treatment of pain. The active ingredient of Belbuca® is buprenorphine.

B. Orange Book Patents

1. The '019 Patent

BDSI is the licensee of U.S. Patent No. 7,579,019 ("the '019 patent") entitled "Bioerodable Film for Delivery of Pharmaceutical Compounds of Mucosal Surfaces." The '019 patent is a continuation of U.S. Patent Nos. 5,800,832 and 6,159,498, which are incorporated by reference in the patents-in-suit (collectively with the '019 patent, the "Tapolsky Patents"). The '019 patent identifies as inventors Drs. Gilles Tapolsky and David Osborne and expired on January 22, 2020. The application which led to the '019 patent first published as U.S. Patent App. Pub. No. 2005/0147658 on July 7, 2005 ("Tapolsky") (DTX-173), assigned on its face to Virotex Corporation.

The Tapolsky patents are directed to bioerodable mucoadhesive ("BEMA") devices that include two film layers: (1) a polymeric diffusion environment (or "mucoadhesive layer")[3] containing the drug, at least one film-forming water-erodible adhesive polymer and at least one bioadhesive polymer, and (2) a backing layer (or barrier layer) to provide a "unidirectional gradient" of the drug toward the mucosal surface and prevent the drug from being swallowed. DFF¶1.[4] The Tapolsky patents are platform technology useful for many categories of drugs, including opioids. For example, the Tapolsky identifies butorphanol as an exemplary opioid for use in the patented BEMA buccal devices. DFF¶2.

2. The '866 and '843 Patents

BDSI is the assignee of the '866 and '843 patents, entitled "Transmucosal Delivery Devices with Enhanced Uptake" and identify as the inventors Drs. Andrew Finn and Niraj Vasisht. The '866 patent issued on April 3, 2012, and the '843 patent issued on May 23, 2017. (*See* JTX-001 and JTX-002, respectively.)

The '866 and '843 patents claim an earliest priority date of July 21, 2006, and August 23, 2006, and expire on July 23, 2027. Both the '866 and '843 patents

[3] A BEMA device includes a mucoadhesive film layer and a non-adhesive backing layer. The parties and experts use the terms "devices" and "films" interchangeably, and the terms "mucoadhesive layer" and "polymeric diffusion environment" interchangeably. (*See, e.g.*, Tr. 131:19-132:13, 648:6-14.)

[4] Citations to "DFF¶__" refer to Alvogen's Proposed Findings of Fact.

claim priority to Int'l Patent App. No. PCT/US2007/016634, which published as WO 2008/011194 ("Vasisht I") (DTX-017). (*See* JTX-001 and JTX-002, respectively.) The parties dispute whether the asserted claims are entitled to claim priority to Vasisht I for purposes of Alvogen's anticipation defense.

The '866 and '843 patents claim a Tapolsky BEMA device containing buprenorphine, wherein the polymeric diffusion environment is buffered to a pH that is optimal, upon introduction of saliva from the buccal surface, for dissolving and ionizing buprenorphine. DFF¶3.

BDSI asserts claims 3, 4, and 5 (which depend from claim 1) and claim 10 (which depends from claim 8) of the '866 patent; and claims 8 (which depends from claim 1), 9 (which depends from claims 1 and 7), and 20 (which depends from claim 13) of the '843 patent.

(a) Prosecution History of the '866 Patent

Application No. 13/184,306, which led to the '866 patent, was filed on July 15, 2011. (JTX-0001-0001.) The '306 application was filed with a Petition to Make Special under Accelerated Examination Program. (JTX-0004-0116-119.) After a rejection, BDSI filed the Declaration of Dr. Andrew Finn. (JTX-0004-0231-36.) The Finn declaration includes a discussion of data pertaining to Suboxone® sublingual tablets and formulations BEMA 1-7. After another rejection, BDSI filed the Declaration of Dr. Niraj Vasisht. (JTX-0004-0286-288.)

The USPTO issued a Notice of Allowance, and the '866 patent subsequently issued April 3, 2012. (JTX-0001-0001.)

(b) Prosecution History of the '843 Patent

Application No. 15/212,912, which led to the '843 patent, was filed On July 18, 2016. (JTX-0002-0001.) In response to a double-patenting rejection, BDSI filed a terminal disclaimer over the '866 patent. After another rejection, BDSI submitted the Declaration of Dr. Niraj Vasisht. (JTX-0005-2769-772.) The declaration purports to address various prior art references. *See* DFF¶¶153-154. The PTO issued a Notice of Allowance, and the '843 patent subsequently issued May 23, 2017. (JTX-0002-0001.)

3. The '539 Patent

BDSI is the assignee of the '539 patent, entitled "Transmucosal Drug Delivery Devices for Use in Chronic Pain Relief," which again identifies as inventors Drs. Finn and Vasisht. The '539 claims a priority date of December 21, 2011, issued on February 27, 2018, and expires on December 21, 2032. (*See* JTX-003.) The parties do not dispute that Vasisht I is prior art to the claims of the '539 patent.

The '539 patent is directed to a Tapolsky BEMA device disclosed in Vasisht I, wherein the backing layer is buffered to a pH of 4.0 to 4.8. DFF¶4. BDSI asserts claims 9 and 20 (which depend from claim 1).

Application No. 13/724,959, which led to the '539 patent, was filed on December 21, 2012. (JTX-0003-0001.) After a series of rejections and responses, on July 26, 2017, applicants filed a Response, along with the Declaration of Niraj Vasisht, Ph.D. under 37 C.F.R. § 1.132. (JTX-0006-4100-102.) After yet another rejection and response, the PTO issued a Notice of Allowance, and the '539 patent subsequently issued on February 27, 2018. (JTX-0003-0001).

C. Alvogen's Paragraph IV Certifications

The patents-in-suit and the '019 patent are listed in the FDA Orange Book entry for Belbuca®. Alvogen filed an ANDA seeking FDA approval to market a generic version of Belbuca® after the expiration of Tapolsky's '019 patent but prior to the expiration of the patents-in-suit. Alvogen's ANDA contains Paragraph IV certifications alleging that the patents-in-suit are invalid. BDSI received notices of Alvogen's Paragraph IV certifications and initiated the present litigation.

III. ALVOGEN'S TRIAL WITNESSES

Alvogen presented the following witnesses at trial in support of its case-in-chief.

A. Dr. Bozena Michniak-Kohn

Dr. Bozena Michniak-Kohn is a Professor of Pharmaceutics at Rutgers University and the Director of its Laboratory for Drug Delivery. (Tr. 82:14-17.) She was qualified as an expert in transmucosal drug delivery without objection. (Tr. 85:5-13.)

Dr. Michniak-Kohn testified about the working mechanisms of a BEMA device, namely that the saliva must dissolve and ionize the drug in order for it to leave the dosage form and become available for permeation through the mucosal membranes and absorption into the bloodstream. Dr. Michniak-Kohn further testified about the scope and content of the prior art. She answered the two binary questions that BDSI admitted were dispositive with respect to the '866 and '843 patents: (1) that it would have been obvious to utilize buprenorphine in Tapolsky's BEMA platform, and (2) that it would have been obvious to buffer the mucoadhesive environment of Tapolsky to the pH values of the asserted claims.

Dr. Michniak-Kohn also testified that the '866 and '843 patents were not entitled to claim a priority date that is earlier than the actual filing date of the '866 patent because the priority applications do not disclose the claimed pH ranges, which BDSI added to the patents-in-suit as new matter. Finally, Dr. Michniak-Kohn testified that Vasisht I inherently discloses the pH values of the backing layer claimed in the '539 patent because the two backing layers are the same and have the same pH as the Belbuca® backing layer.

B. Dr. Steven Shafer

Dr. Steven Shafer is a Professor of Anesthesiology, Perioperative and Pain Medicine at Stanford University, and an Adjunct Associate Professor of Bioengineering and Therapeutic Sciences in the School of Pharmacy at the

University of California in San Francisco. (Tr. 315:19-316:2.) He was qualified as an expert in the field of pharmacokinetics and pharmacodynamics, in particular with respect to opioids, without objection. (Tr. 320:2-4.)

Dr. Shafer testified that the prior art taught the limitations of claims 4 and 5 of the '843 patent. Dr. Shafer also testified that Vasisht I taught the adverse event limitations in claims 9 and 20 of the '539 patent. Finally, Dr. Shafer testified that Vasisht I and Reder taught the steady-state Cmax limitation of claim 20 of the '539 patent.

C. Dr. Perry Fine

Dr. Perry Fine is a Professor of Anesthesiology at the University of Utah, with a clinical practice specializing in pain medicine, hospice, and palliative medicine at the University's Pain Management and Research Center. (Tr. 476:14-18, 477:13-19.) Dr. Fine is Board-certified in anesthesiology with subspecialty Boards in pain medicine. (476:23-477:3.) He was qualified as an expert in the treatment of pain, anesthesiology, and administration of opioids and other therapies to manage pain, without objection. (Tr. 479:12-17.)

Dr. Fine testified about the history and properties of buprenorphine known prior to the patents-in-suit. Dr. Fine also testified regarding the adverse event profiles of various drug products, including Butrans® and Belbuca®. Dr. Fine testified that the adverse event profiles associated with buprenorphine-containing

drugs, such as respiratory depression, are the result of characteristics of buprenorphine itself. Dr. Fine also testified that the claimed subject matter did not solve any purported long-felt needs identified by BDSI.

IV. PERSON OF ORDINARY SKILL IN THE ART ("POSA")

The level of ordinary skill in the art is informed by the educational level of workers in the field. *In re GPAC Inc.*, 57 F.3d 1573, 1579-80 (Fed. Cir. 1995) (affirming that the level of ordinary skill "was best determined by appeal to the references of record"). POSAs in this case include Tapolsky, Bullingham, Cassidy, Todd, the Suboxone® formulators and other authors of the prior art that pertain to the issues presented at trial.

Dr. Michniak-Kohn testified that a POSA would have a bachelor's degree in pharmaceutical sciences, chemistry or related field, plus three to five years of relevant experience in developing transmucosal dosage forms. Alternatively, such person would have a Ph.D. in one of those fields and less practical experience. DFF¶5.

This POSA definition applies to all relevant issues in this case. At trial, BDSI did not object to this description of a POSA and Dr. Williams testified that his opinions on behalf of BDSI would not change in view of this definition of a POSA. DFF¶6. Furthermore, BDSI did not object to any expert's testimony regarding the knowledge and motivation of such a POSA on the grounds the

characteristics of the POSA were improperly defined. Accordingly, there is no dispute about the characteristics of the POSA in the context of the patents-in-suit and knowledge and motivations in view of the prior art.

V. THE ASSERTED CLAIMS OF THE '866 AND '843 PATENTS ARE OBVIOUS

The '866 and '843 patents claim Tapolsky's BEMA device containing buprenorphine in the mucoadhesive layer buffered to an optimal pH and the inherent pharmacokinetic properties of such a device.

A. Statement of Law

A patent "may not be obtained … if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2012) (pre-AIA).

Obviousness is a question of law based on four underlying factual determinations: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of nonobviousness. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

An obviousness determination asks for "the existence of a motivation to combine elements from different prior art references" and whether "a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).[5]

B. Scope and Content of the Prior Art

The prior art admitted into evidence "includ[es] 'that reasonably pertinent to the particular problem with which the inventor was involved.'" *In re GPAC Inc.,* 57 F.3d 1573, 1577 (Fed. Cir. 1995) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535 (Fed. Cir. 1983)). At trial, BDSI did not dispute the relevance of any of the prior art admitted into evidence. Specifically, BDSI raised no objection that the admitted prior art "relates to the same problem as that addressed by the claimed invention" *(id*. at 1578), and BDSI did not attempt to rebut the presumption that a POSA was "aware of all the pertinent prior art" admitted into evidence. *Standard Oil Co. v. Am. Cyanamid Co*., 774 F.2d 448, 454 (Fed. Cir. 1985)).

[5] See D.I. 230, Ex.5A at ¶¶108-145 for additional law on obviousness.

1. Brief History of Buprenorphine

Buprenorphine, discovered in 1966, is an opioid analgesic known to treat acute and chronic pain. DFF¶7. The history of buprenorphine is generally set forth in the following timeline:

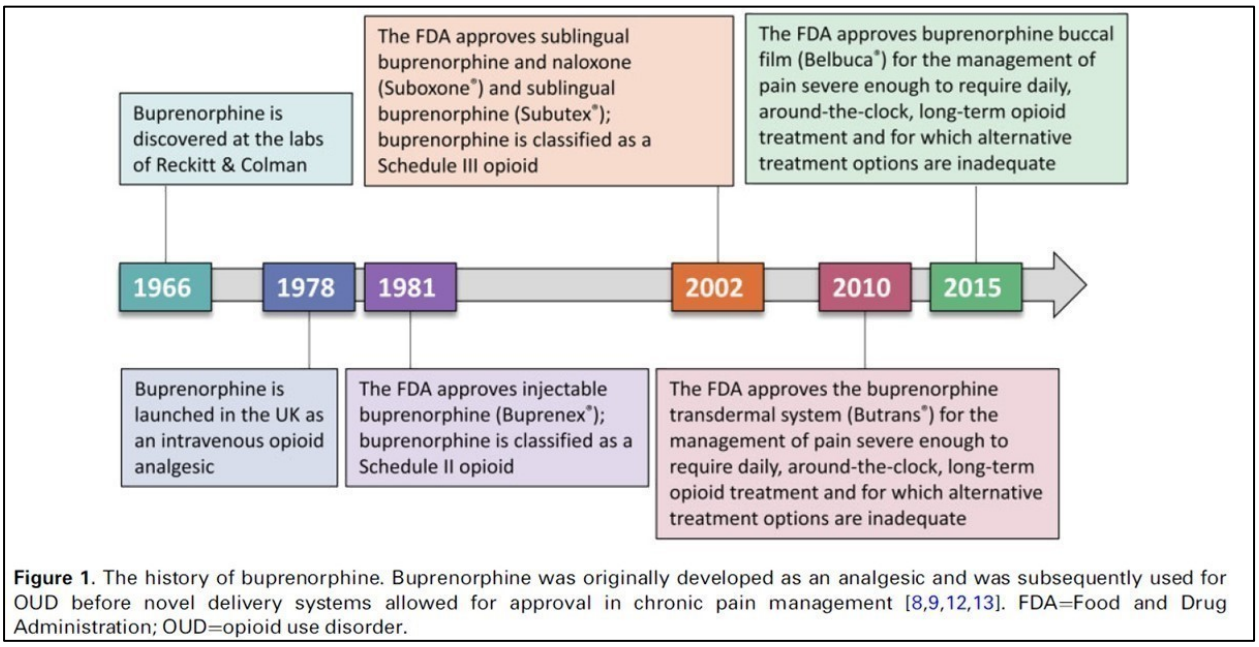


Figure 1. The history of buprenorphine. Buprenorphine was originally developed as an analgesic and was subsequently used for OUD before novel delivery systems allowed for approval in chronic pain management [8,9,12,13]. FDA=Food and Drug Administration; OUD=opioid use disorder.

DDX 1-10; DFF¶8. POSAs knew buprenorphine to have "high first pass effect,"[6] which means that the liver destroys and renders the buprenorphine less effective if swallowed. DFF¶9. Because of its known first pass effect, POSAs have formulated buprenorphine as injections, nasal sprays, sublingual tablets and buccal films. DFF¶10.

[6] The terms "first pass effect" and "first pass metabolism" are used interchangeably in the prior art and herein.

2. Prior Art Specific to BEMA Delivery of Opioids

BEMA devices deliver drugs directly to the oral mucosa and thus avoid first pass metabolism. DFF¶11. Dr. Michniak-Kohn testified about the working mechanism of BEMA devices. DFF¶12. Generally, the user applies the BEMA device to the cheek inside the buccal surface. DFF¶12. Saliva[7] activates the mucoadhesive polymers, causing the device to adhere to the buccal surface. DFF¶12. As the saliva penetrates the device, the pH buffers dissolve in the saliva and lower its pH, allowing it to dissolve and ionize the buprenorphine. DFF¶12. The dissolved and ionized buprenorphine then moves through the mucoadhesive layer by concentration gradient and permeates the mucosal surface, where it is absorbed into the bloodstream. DFF¶12.

(a) Tapolsky (2005)

Tapolsky discloses the BEMA devices incorporated by reference and claimed by the patents-in-suit. DFF¶15. Specifically, Tapolsky discloses a BEMA device for any active agent, such as opioids like butorphanol[8] that would benefit from transmucosal delivery. DFF¶¶16-17.

Tapolsky's BEMA device contains an adhesive layer including a film-forming water erodible polymer, such as hydroxyethyl cellulose or hydroxypropyl

[7]Saliva and mucous (or mucus) are used interchangeably herein. Each is predominantly water. DFF¶13.

[8] The patents-in-suit also disclose butorphanol as an exemplary opioid. DFF¶18.

cellulose, and a bioadhesive polymer, such as sodium carboxymethylcellulose. DFF¶22. Tapolsky's polymers for the adhesive layer are the same polymers described in the patents-in-suit and utilized in Belbuca®. DFF¶23.

Tapolsky's BEMA device also contains a non-adhesive backing layer to provide unidirectional delivery of the drug towards the mucosal surface and to minimize swallowing. DFF¶¶24-25. Tapolsky discloses suitable polymers for the backing layer, including a water-erodible, film-forming polymer such as hydroxyethyl cellulose or hydroxypropyl cellulose. DFF¶26. Tapolsky's polymers for the backing layer are the same polymers described in the patents-in-suit and utilized in Belbuca®. DFF¶27.

Tapolsky's BEMA devices "yield fast onset of activity, excellent bioavailability, and sustained delivery" (DFF¶28) and provide drug delivery that achieves effective concentrations beyond four hours. DFF¶29.

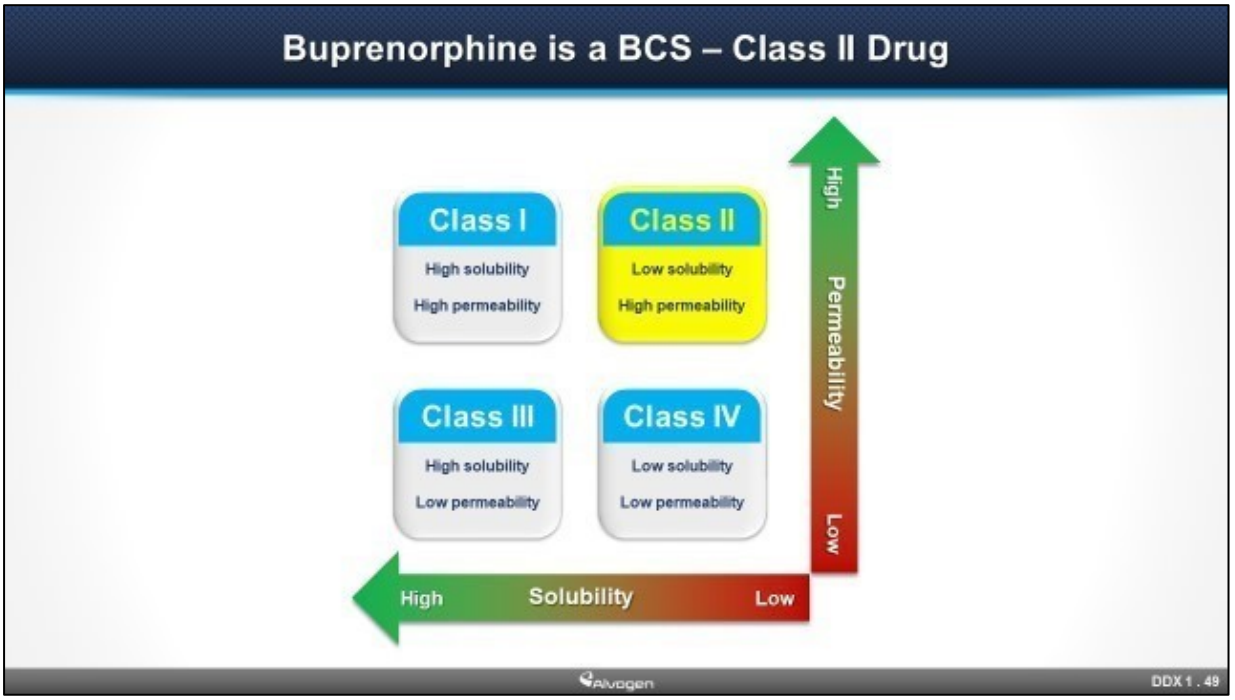
(b) Moro (2003)

Like Tapolsky, Moro discloses BEMA devices incorporated by reference by the patents-in-suit. DFF¶30. Moro specifically discloses BEMA delivery of buprenorphine. DFF¶¶31-32. The device contains an adhesive layer including a film-forming polymer and a bioadhesive polymer. DFF¶33. The device also contains a non-adhesive backing layer including a film-forming polymer, which maximizes unidirectional delivery of drug toward the mucosal surface while

minimizing swallowing of the drug. DFF¶34. Moro's polymers for the mucoadhesive and backing layers are the same polymers described by Tapolsky and the patents-in-suit, and utilized in Belbuca®. DFF¶¶22-23, 26-27, 33-35.

3. Prior Art Specific to Buprenorphine Properties

Buprenorphine hydrochloride[9] is the salt form of buprenorphine used in pharmaceutical formulations. DFF¶36. Buprenorphine is a BCS-II ("Biopharmaceutics Classification System – Class II") drug, which means that the drug has low water solubility but high permeability (lipophilicity). DFF¶37.



[9] The terms "buprenorphine" and "buprenorphine hydrochloride" are used interchangeably herein.

In other words, if the formulation buffers the saliva to a pH capable of ionizing and dissolving the buprenorphine, then the buprenorphine will readily permeate the mucosal membranes and absorb into the bloodstream. DFF¶38.

(a) Johnson (2005)

Johnson summarizes what POSAs knew about buprenorphine prior to the patents-in-suit. Specifically, that buprenorphine: (1) is a highly potent and effective analgesic with a long duration of action; (2) has a wider safety profile compared to other opioids, especially with regard to respiratory depression; (3) has low abuse potential and fewer symptoms of withdrawal; (4) experiences high first pass effect (and should be administered transmucosally, for example, to avoid liver metabolism); and (5) is extremely lipophilic (meaning that it will permeate mucosal membranes when dissolved and ionized). DFF¶¶39-40.

(b) Bullingham I (1981)

Bullingham I discloses the same properties of buprenorphine described in Johnson (e.g., that buprenorphine is highly lipophilic). DFF¶¶26, 43. Bullingham teaches that sublingual delivery of buprenorphine is effective because of the "specific features of buprenorphine." DFF¶41. Bullingham teaches that sublingual administration provides quantifiable concentrations of buprenorphine between 40 and 60 minutes and an onset of analgesia of between 15 and 45 minutes. DFF¶42. Bullingham also teaches that the sublingual administration of

buprenorphine achieves effective buprenorphine concentrations for more than four hours. DFF¶45.

4. Prior Art Specific to pH

Saliva is not ideal for dissolving buprenorphine due to its near-neutral pH. DFF¶46.[10] POSAs understood buprenorphine to be poorly soluble in saliva. DFF¶48. POSAs also understood that buprenorphine solubility is highly pH-dependent, having the highest solubility at low (acidic) pH values. DFF¶49.[11] At these low pH values, buprenorphine is nearly 100% ionized.[12] DFF¶52. The entire prior art of record demonstrates that formulators provided buprenorphine in acidic pH environments where it is ~100% ionized. DFF¶54. The trial record includes not a single reference, prior art or otherwise, where a formulator attempted to provide buprenorphine in a neutral or basic environment, or where the buprenorphine was less than ~100% ionized. DFF¶¶55-56.

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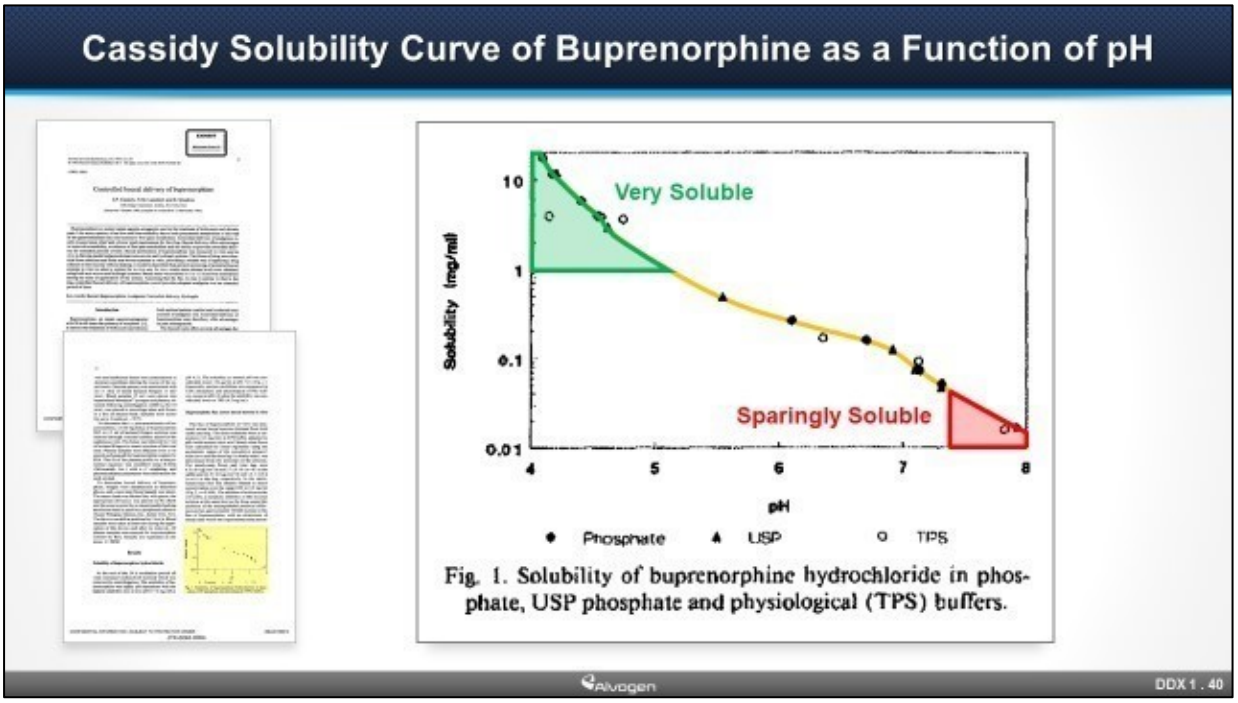
[10] pH is the measure of how acidic or basic a liquid is relative to neutral water. DFF¶47. pH is logarithmic, such that, for example, a pH of 4 is 10X more acidic than a pH of 5 and 100X more acidic than a pH of 6. DFF¶47.

[11] "Solubility" is the maximum concentration of drug than can dissolve in a solvent (e.g., water). DFF¶50. "Dissolution" is the rate the drug dissolves in the solvent. DFF¶51.

[12] "Ionization" is the process by which the neutral drug salt converts to electrically charged "ions" in solution. DFF¶53. Like solubility, ionization can be highly pH-dependent. DFF¶53.

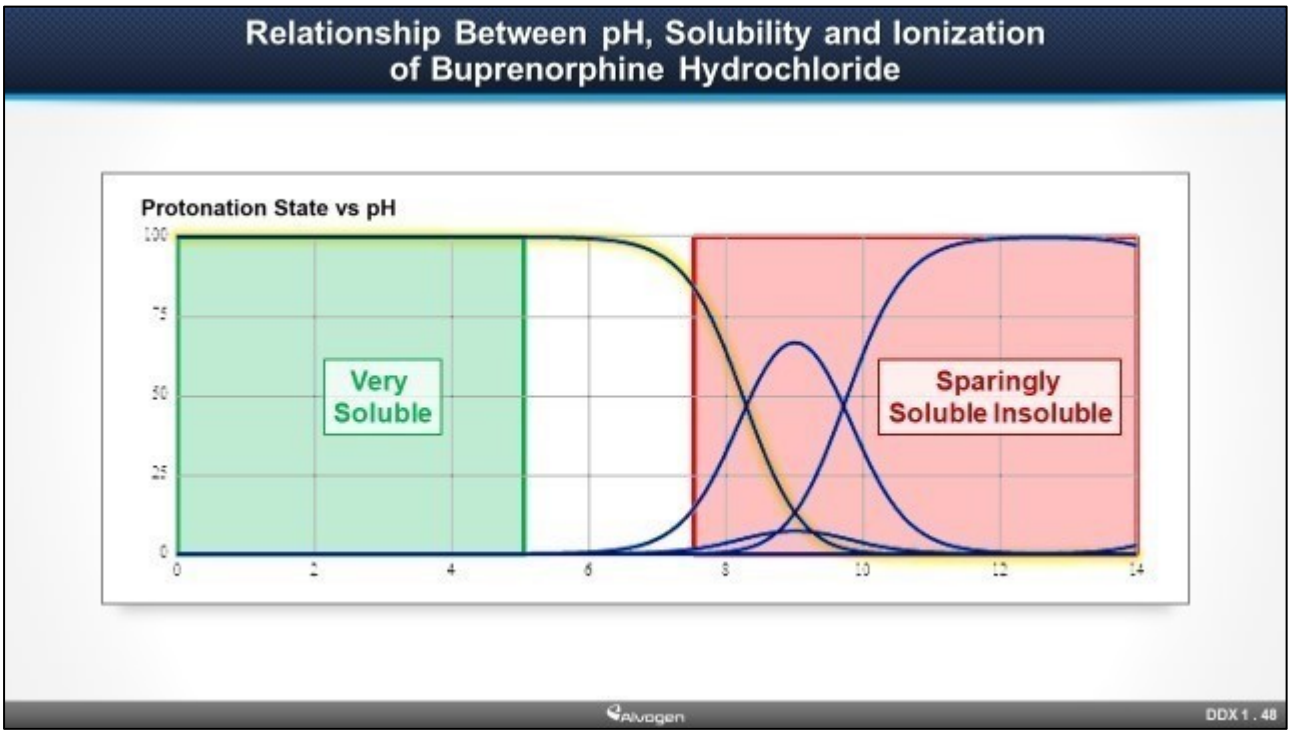
(a) Cassidy (1993)

Cassidy teaches that the solubility of buprenorphine is highly pH dependent, with the highest solubility seen at low pH. [13] DFF¶¶57-63. Figure 1 of Cassidy (as annotated by Dr. Michniak-Kohn) illustrates that buprenorphine is "very soluble" at pH values below 5, and is "sparingly soluble" to insoluble at pH values above 7.5. DFF¶64.



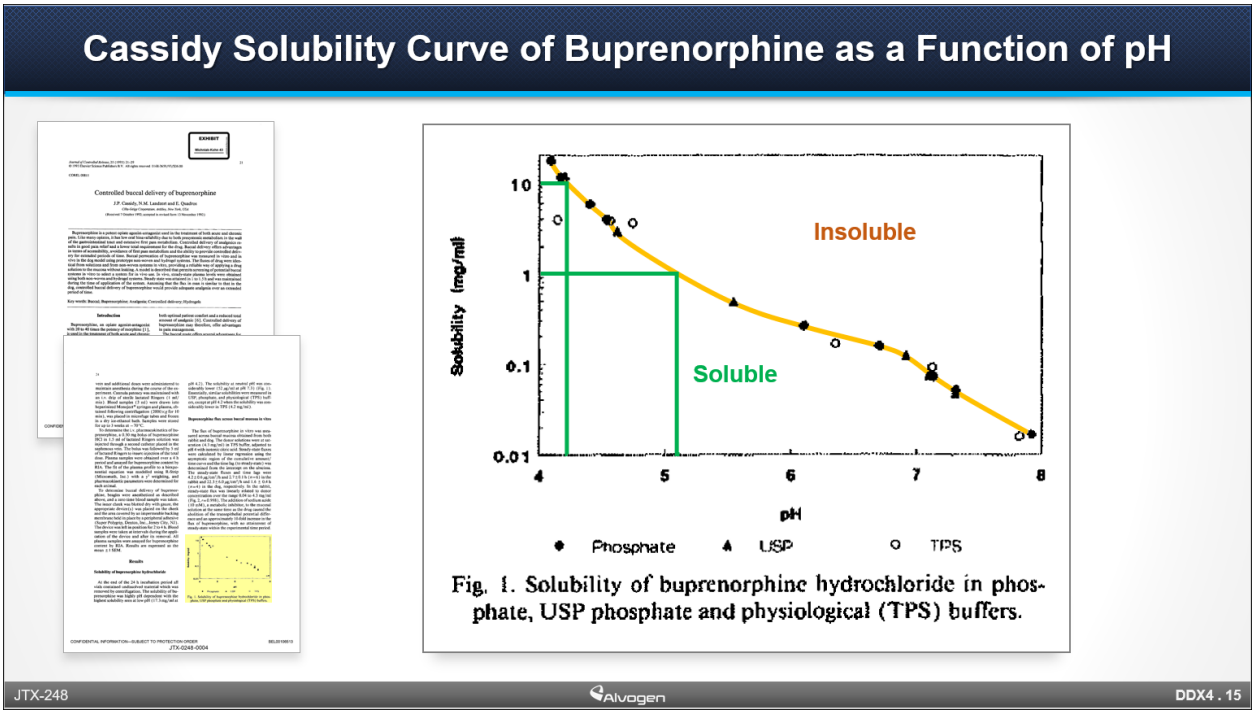
[13] Cassidy was found to teach a POSA that transmucosal absorption occurs at acidic pHs in connection with Judge Andrews' decision holding the asserted claims of U.S. Patent 8,475,832 ("the '832 patent") obvious. *See Reckitt Benckiser Pharms. Inc. v. Watson Labs., Inc.*, C.A. No. 13-1674-RGA, 2016 WL 3186659, at *10 (D. Del. June 3, 2016). The '832 patent was listed in FDA's Orange Book for Suboxone® Sublingual Film. *Id.* at *1-2. Judge Andrews further found that a POSA would have "credited" data demonstrating that buprenorphine is absorbed transmucosally at pH values within or near the claimed range (i.e., about 3-3.5) "over general implications of pH Partition Theory." *Id.* at *10.

As Dr. Michniak-Kohn testified, based on the calculations performed by Dr. Stephen Davies (BDSI's chemistry expert), a POSA would have understood that buprenorphine is 100% ionized at the pH values below 5 where it is "very soluble." DFF¶¶65-66.



Cassidy further illustrates that buprenorphine solubility increases exponentially[14] as pH decreases from 5 to 4, which anticipates the claimed pH ranges in the patents. DFF¶67.

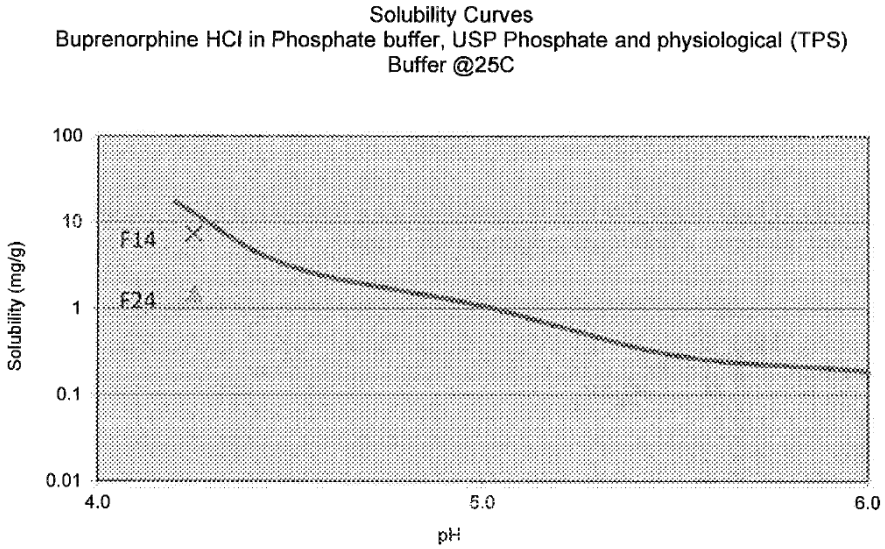
[14] A 10-fold increase in solubility per one unit drop of pH represents an exponential increase in solubility. DFF¶¶68-69.



The BDSI formulators understood the implications of Cassidy. As shown in BDSI's own development, which replicates Cassidy's data, the final commercial formulations (F14 and F24) were "formulated in the pH of highest [aqueous] solubility" as well as at concentrations lower than the solubility limit of the polymeric casting solution.[15] DFF¶68.

[15] During manufacture, buprenorphine and the polymers dissolve in water ("polymeric casting solution"), which is later removed during the drying process. DFF¶72. A POSA would also know that in the final product, buprenorphine exists as a solid and, as such, it must dissolve and ionize in the saliva in order to leave the dosage form and permeate the membrane. DFF¶72. The solubility of buprenorphine in the polymer is not relevant to the requirement that buprenorphine be soluble in saliva. DFF¶72.

Figure 6 The concentration of F24 and F14 Formulations as a function of pH and comparison to the Journal of Controlled Release, Volume 25, pages 21-29, 1993.



In addition to the literature comparison, the solubility of buprenorphine in the mucoadhesive blend was explored at different pH conditions. F14 and F24 mucoadhesive blend formulations were formulated in the pH of highest solubility and at concentrations lower than the solubility limit as shown in Figure 7. As a result, the particle size for the API is not a critical attribute.

(DTX-370-019.)

(b) Weinberg (1988)

Weinberg teaches that buprenorphine has the highest partition coefficient (and is the most lipophilic) as compared to eight other known opioids. DFF¶73.

Table I. The concentration, partition coefficient, and pKa of study opioids

Drug	*Concentration (mg/ml)*	*PC**	*pKa†*
Morphine	5.0	0.00001	7.9
Hydromorphone	1.0	0.0001	NA
Levorphanol	1.0	0.01	9.4
Heroin	2.5	0.04	NA
Fentanyl	0.05	19.6	8.4
Methadone	5.0, 0.8	44.6	9.3
Buprenorphine	0.1	60.3	NA
Oxycodone	2.5	NA	NA
Naloxone	1.0	NA	7.9

PC, partition coefficient; NA, not available.
Partition coefficients and pKa values compiled from references 15 through 18.
*Heptane and phosphate buffer at pH 7.4.
†At 37° C.

(JTX-249-002.)

A POSA would have expected buprenorphine, in its fully ionized form, to permeate the lipid environment of the mucosal membrane. DFF¶74. Weinberg reports that buprenorphine, at pH 6.5, where a POSA would have known buprenorphine to be nearly 100% ionized, absorbs well across the oral mucosa. DFF¶75. Weinberg teaches that the poor solubility of buprenorphine at pH 6.5 prohibits the formulation of buprenorphine at higher, basic pH values. DFF¶76.

(c) Todd (1983)

Todd states, "[b]uprenorphine is a potent antagonist analgesic with good bioavailability following sublingual administration, useful in the relief of moderate to severe pain and also in the treatment of narcotic addiction." DFF¶77.

Todd teaches aqueous (water-based) solutions of buprenorphine for sublingual administration having a finite number of acidic pH values (pH 4, 5, and 6), each of which provide "uptake," i.e., permeation and absorption, of

buprenorphine. DFF¶¶79-81. Todd also includes examples of buprenorphine formulations buffered to a pH between 4.5 and 5.5, where a POSA know buprenorphine to be 100% ionized. DFF¶82. Todd also discloses citric acid/sodium citrate buffers, the same buffers used in Belbuca®. DFF¶83.

At trial, Dr. Williams criticized Todd because the aqueous solutions utilize water and ethanol as co-solvents. DFF¶84. However, Tapolsky teaches that its device, before drying, preferably includes a combination of water and ethanol as co-solvents. DFF¶85. The patents-in-suit also describe water as the solvent before drying, and do not preclude the use of ethanol as a co-solvent. DFF¶86. Furthermore, the patents-in-suit prefer ethanol as a disintegration aid that can be included in the claimed buprenorphine devices to "increase the disintegration rate and shorten the residence time of the device …." DFF¶86. Consequently, Dr. Williams' criticism of Todd actually supports the conclusion that a POSA would combine the teachings of Tapolsky and Todd.

(d) Commercial Suboxone® Sublingual Tablets (2002)

In 2002, FDA approved Suboxone® sublingual tablets. DFF¶87. As noted in the product label, Suboxone® includes buprenorphine and pH buffers (citric acid/sodium citrate).[16] DFF¶88. A POSA would have understood that the pH

[16] Citric acid and sodium citrate are the same buffers used in Belbuca®. DFF¶89.

buffers in Suboxone® would reduce the pH of saliva to allow it to dissolve and ionize the buprenorphine. DFF¶90.

BDSI submitted the Declaration of Dr. Maureen Reitman to the PTO in the context of an *Inter Partes* Review, where BDSI sought to establish the pH of Suboxone® in order to invalidate a competitor's patent. DFF¶91. Following a simple, well-accepted procedure, Dr. Reitman determined that Suboxone® tablets provide a pH of 3.5 in solution. DFF¶¶92-93. BDSI admitted to the PTO that the pH of Suboxone® was inherent to the tablets and known. According to BDSI, the pH "can be readily obtained in a matter of minutes by anyone with deionized water and a pH meter." DFF¶94. The trial record demonstrates that a POSA would have understood that Suboxone®, at a pH of 3.5, provides transmucosal absorption of 100% ionized buprenorphine.[17] DFF¶95.

(e) Birch (2005)

Birch discloses aqueous buprenorphine solutions, which can "induce rapid and prolonged analgesia when delivered intranasally to a patient." DFF¶96. The solutions have a pH between 3 and 4.8, where a POSA would have understood

[17] In the *Reckitt Benckiser* decision on the '832 patent, Judge Andrews held that Suboxone® sublingual tablets "included a sodium citrate and citric acid buffer that was effective in a pH range of 3.0 to 6.2". *Reckitt Benckiser Pharms.*, C.A. No. 13-1674-RGA, 2016 WL 3186659 at *9.

buprenorphine to be 100% ionized, and provide "rapid uptake" of buprenorphine across the nasal mucosa into the bloodstream.[18] DFF¶97.

C. Claims 3 and 10 of the '866 Patent and Claims 8, 9, and 20 of the '843 Patent Are Obvious

Dr. Michniak-Kohn testified that the BEMA delivery device of Tapolsky satisfies all requirements of claims 3 and 10 of the '866 patent, and claims 8, 9, and 20 of the '843 patent, except that Tapolsky does not disclose buprenorphine, and does not disclose that the polymeric diffusion environment is buffered to the claimed pH ranges. DFF¶¶15-29, 98. BDSI did not offer any contrary testimony regarding the disclosure of Tapolsky. DFF¶99. The evidence adduced at trial establishes that it would have been obvious to (1) utilize buprenorphine in Tapolsky's BEMA platform, and (2) buffer Tapolsky's polymeric diffusion environment to the claimed pH ranges, which are optimal for buprenorphine delivery.

1. It Was Obvious to Utilize Buprenorphine in Tapolsky

To determine whether there was a motivation in the art to utilize buprenorphine in Tapolsky's BEMA platform, the Court should "look to interrelated teachings of multiple patents; the effects of demands known to the

[18] As with Cassidy, Birch was also held by Judge Andrews to teach that transmucosal absorption of buprenorphine takes place at acidic pHs in concluding that the '832 patent was obvious. *See Reckitt Benckiser*, C.A. No. 13-1674-RGA, 2016 WL 3186659, at *10.

design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art." *See, e.g., KSR*, 550 U.S. at 418.

A POSA would have been motivated to use buprenorphine in Tapolsky's BEMA platform because the prior art taught its formulation in a BEMA device for buccal delivery. DFF¶¶100-112. A POSA would have known from Johnson, Bullingham I, and Cassidy that buprenorphine is a potent opioid analgesic that experiences high first pass effect requiring transmucosal or other delivery that avoids liver metabolism. DFF¶¶103-105. POSAs believed that a "mucoadhesive delivery system" generally, and BEMA devices specifically, could improve bioavailability by providing unidirectional delivery that avoids loss due to swallowing. DFF¶¶106-111. The Finn declaration comparing BEMA devices to Suboxone® sublingual tablets corroborates this knowledge. DFF¶¶106-111, 143.

Tapolsky and Moro teach that BEMA devices can transmucosally deliver opioids generally, and Moro teaches buprenorphine specifically. DFF¶112. Known therapeutic ranges for buprenorphine were 300-600 µg for injection and 200-400 µg for sublingual tablets. DFF¶¶78, 113. Providing an effective amount of an opioid like buprenorphine in the BEMA devices of Tapolsky or Moro was a matter of routine skill. DFF¶114.

2. It Was Obvious to Buffer Tapolsky to the Claimed pH

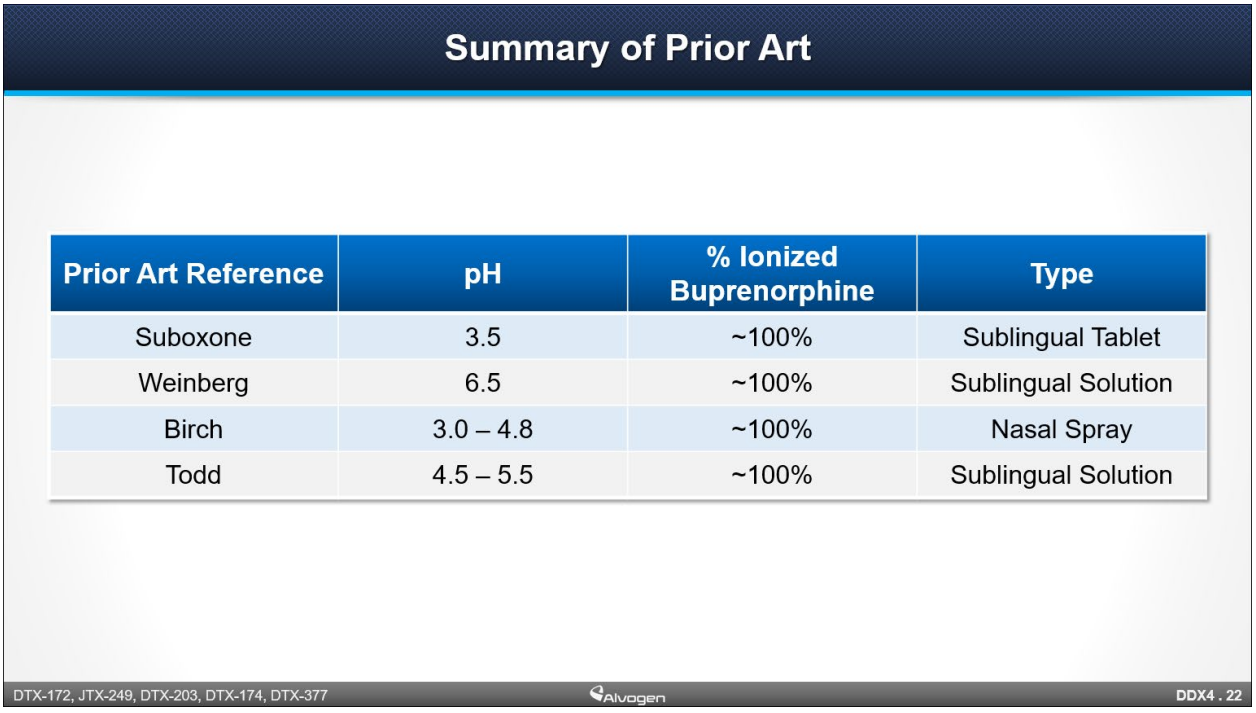
Claims 3 and 9 of the '866 patent are directed to Tapolsky's BEMA device containing buprenorphine buffered to a pH "between about 4.5 and about 5 [or 5.5]." DFF¶115. Claims 8, 9 and 20 of the '843 patent are directed to Tapolsky's BEMA device containing buprenorphine buffered to a pH "between about 4 and about 6 [or 7.5]." DFF¶115. These claims would have been obvious in view of Tapolsky (or Moro) and Todd.

Basic science and common sense dictates that buprenorphine must dissolve from the BEMA device into the saliva before it can permeate the mucosa. DFF¶116. Dr. Williams acknowledged this fact. DFF¶116. He also acknowledged that buprenorphine is a BCS-II drug, and that a POSA would have known that buprenorphine would permeate the mucosa if dissolved and ionized—such as in saliva buffered to a pH between 4 and 5. DFF¶117.

There is no dispute that the solubilization of buprenorphine from a BEMA device is highly pH dependent. DFF¶118. In addition, there is no dispute that buprenorphine must ionize in order to dissolve, and its ionization is likewise highly pH dependent. DFF¶119. Cassidy shows that the solubility of buprenorphine increases exponentially as pH drops from 5 to 4, where it remains 100% ionized. DFF¶121. A POSA would have expected that a polymeric diffusion environment of Tapolsky buffered to a pH around these values would provide the highest

amount of dissolved and ionized buprenorphine to be available for absorption. DFF¶¶122-123.

The prior art corroborates this expectation—pH values of 3-4.8 (Birch), 3.5 (Suboxone®), 4-5 (Cassidy), 4-6 (Todd), and 6.5 (Weinberg). DFF¶124. Regardless of dosage form, prior art transmucosal formulations provide buprenorphine at acidic pH where it is dissolved and ~100% ionized, and demonstrate its absorption. DFF¶124.



Therefore, the prior art confirms that a POSA would have expected dissolved and ionized buprenorphine to readily permeate mucosal membranes at these acidic pH values. DFF¶¶124-125.

The prior art taught that buffer systems maintain active agents in their ionized form to help "overcome the influence of the conditions of the surrounding environment, such as rate of saliva secretion, pH of the saliva, and other factors." DFF¶127. Because the pH of saliva varies from 5.8 to around 7, which is not ideal for dissolving buprenorphine, a POSA would provide buffers in the polymeric diffusion environment that acidify the saliva. DFF¶126.

POSAs knew how to buffer transmucosal formulations for this purpose. DFF¶128. For example, both Todd and Suboxone® include citric acid and sodium citrate buffers—the same buffers in Belbuca®. DFF¶128. Just as BDSI did for Belbuca®, a POSA would have copied the acidifying buffers of Todd and Suboxone® in formulating Tapolsky's BEMA device for buprenorphine delivery. DFF¶128.

3. There Are No Surprising or Unexpected Results

Before the PTO and at trial, BDSI contended that the acidic pH of Belbuca® surprisingly and unexpectedly results in higher absorption of buprenorphine. (*See* DFF¶¶142-144.) However, there is nothing surprising or unexpected in the improved bioavailability of a BEMA device buffered to the pH values of Cassidy where buprenorphine solubility increases exponentially. *See* DFF¶67. There is nothing surprising or unexpected that these optimal values from Cassidy are also the optimal values for buprenorphine dissolution and ionization from Tapolsky's

BEMA device. *See* DFF¶¶51, 53, 65. There is nothing surprising or unexpected that these optimal values provide for buprenorphine absorption in view of all of the prior art using similar pH values regardless of the buprenorphine formulation. *See* DFF¶54.

From the very beginning, BDSI provided false information to the PTO. In the '866 patent, BDSI submitted a petition requesting accelerated examination and misrepresented that Tapolsky does "not teach administration of an opioid." DFF¶141. This is remarkable given that BDSI had a license to Tapolsky at the time. This statement was proven to be false at trial when experts from both sides confirmed that Tapolsky discloses butorphanol, which is an opioid, as suitable for use in the BEMA platform. DFF¶141.[19] The record shows no challenge to this false assertion by the PTO.

In addition, during prosecution of the '866 patent, BDSI submitted the Finn Declaration, where Dr. Finn falsely stated that Suboxone® was unbuffered. As testified to by Dr. Michniak-Kohn, and as admitted by Dr. Williams, Suboxone®

[19] Later, during the prosecution of the '843 patent, the Vasisht Declaration argued that the Todd reference was not relevant because buprenorphine solutions "may merely migrate to another aqueous solution, the saliva." DFF ¶¶153-154. This is clearly misleading because Todd addresses the "uptake of the drug" (i.e., permeation and absorption) and does not refer to buprenorphine merely migrating into saliva. DFF ¶154.

contains the same citric acid/sodium citrate buffers described in the patents-in-suit and utilized in Belbuca®. DFF¶146.

Dr. Finn also falsely stated that the pH of Suboxone® was "N/A," meaning either that the pH was "not available" or "not applicable." However, the pH of Suboxone® was both available and applicable. As admitted by BDSI in another PTO proceeding, Suboxone® was buffered to a pH of 3.5. DFF¶¶91-92, 146.

This was a material misrepresentation. That Suboxone® (just like all of the other prior art) was effective at an acidic pH contradicts Finn's statement that the increased bioavailability at lower pH values was "unexpected and could not have been predicted from a mere change in pH[.]" Instead, the prior art predicted that BEMA devices, such as Tapolsky's, would increase the bioavailability of buprenorphine due to the direct application of buprenorphine to the mucosa without it being swallowed. *See* DFF¶24. It was not pH but the BEMA device itself that was an improvement over the Suboxone® tablets. And all of the prior art provided buprenorphine in an acidic environment in order to optimize its dissolution, ionization and permeation/absorption. DFF¶54. Consequently, any improvement over Suboxone® is attributable to Tapolsky's BEMA device, not the selection of an optimal pH.

Furthermore, at the time that the '866 patent was filed, BDSI had only formulated BEMA 1 (pH 7.25) and BEMA 2 (pH 6.0). DFF¶149. As confirmed

by BDSI's expert Dr. Thisted, there was no statistically significant difference between BEMA 1 and BEMA 2 with respect to either Cmax or AUC. DFF¶151. This is not surprising in view of Cassidy's solubility data. Yet, based on no difference between BEMA 1 and 2, Dr. Finn predicted and preferred pH values that were much lower—i.e., pH values between 4 and 6, specifically pH 4.5-5. Dr. Finn apparently made that prediction without any predicate data.

Dr. Finn was not a profound visionary. Based on what was then known about buprenorphine, such as Cassidy's teaching that shows an exponential increase in solubility at these acidic pH values,[20] any POSA using routine skill would have buffered this drug at a pH between 4 and 6. Although Dr. Finn must have known about Cassidy in view of BDSI's contemporaneous development reports that relies on Cassidy's teachings, he never acknowledged Cassidy in his declaration. *See* DFF¶70. In all events, a POSA would have known about Cassidy even though the PTO did not.

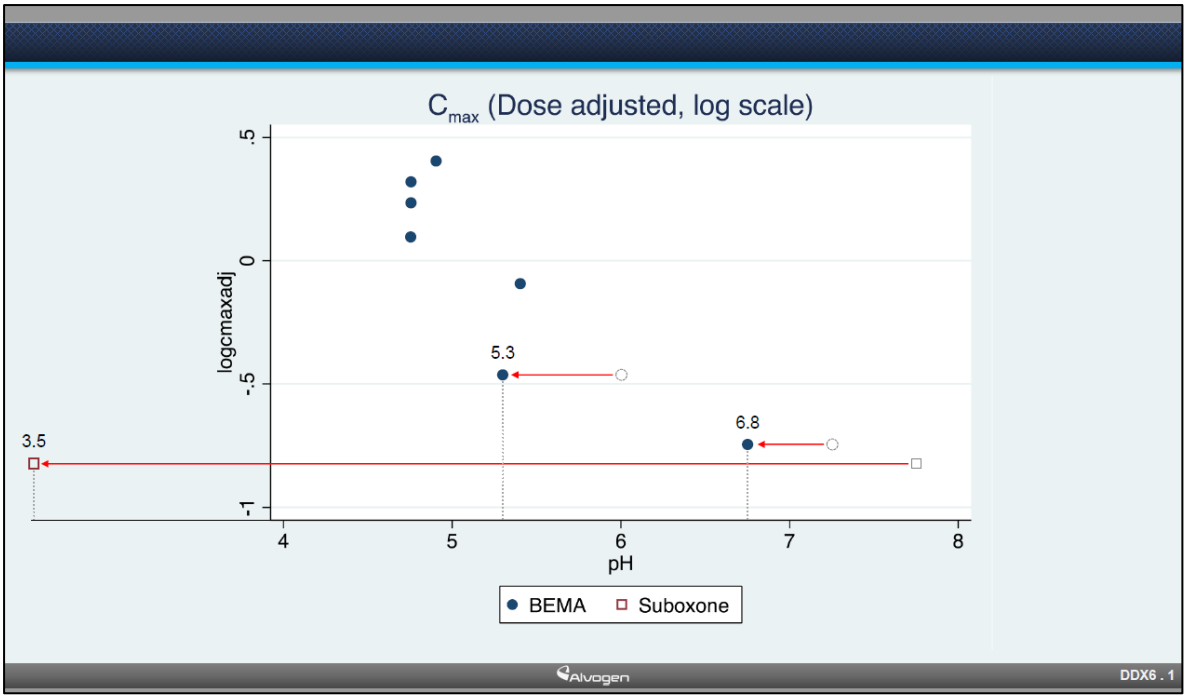
Dr. Finn also falsely stated that the pH of the BEMA 1 formulation is 7.25 and the pH of the BEMA 2 formulation is 6. As confirmed by documents BDSI submitted to FDA, the actual pH of BEMA 1 is 6.8 and the actual pH of BEMA 2

[20] The trial record demonstrates that a POSA, and the inventors, would have relied on the pH dependent solubility of buprenorphine in pre-formulation studies, such as the data taught by Cassidy, because, during the development of Belbuca®, BDSI did just that. DFF¶70.

is 5.3. DFF¶147. Again, this was a material misrepresentation of a fact. With the correct pH values for BEMA 1 and BEMA 2, the data presented no longer supports the claimed pH range of 4-7.5 (claim 9). The justification for the high end in asserted claim 9 vanishes if the BEMA 1 device does not actually have the stated pH.

BDSI also did not inform that PTO that there was no statistically significant difference between BEMA 1 and BEMA 2. *See* DFF¶151. That alone entirely refutes Dr. Finn's conclusion that "a pH of between 4 and about 6 exhibit dramatically improved C_{max} and/or bioavailability as compared to devices having a polymeric diffusion environment at a pH of 7.25 or those having no buffered environment[.]" *See* DFF¶143. The differences between BEMA 1 and BEMA 2 may have been due purely to chance. DFF¶151.

Furthermore, as can be seen in the demonstrative exhibit below, using the correct pH values for BEMA 1, BEMA 2 and Suboxone® disrupts any alleged trend in the data from the Finn Declaration, particularly for pH values below 6. The BEMA 2 device with an actual pH of 5.3 had lower bioavailability than its next nearest neighbor, which is the opposite of the supposed "surprising and unexpected" trend. Because BDSI withheld the actual pH data during prosecution, the PTO never had an opportunity to consider it.



DFF¶152. What these data actually show is that the optimal pH value for buprenorphine BEMA delivery is precisely the same pH value taught by Cassidy, where there is an exponential increase in buprenorphine solubility as pH drops below 5. It also shows that any improvement over Suboxone® sublingual tablets is due to Tapolsky's BEMA device, not pH.

Based on Cassidy's teaching that the solubility of buprenorphine exponentially increases as pH drops below 5, and considering Todd's teaching of buprenorphine "uptake" (absorption) at acidic pH values (4.5-5.5), it was unsurprising and completely expected that the absorption of buprenorphine would be maximized within the claimed ranges of 4.5-5, 4.5-5.5, 4-6 and 4-7.5. DFF¶145, *see also* DFF¶8.)

D. Claims 4 and 5 of the '866 Patent Are Obvious

Claims 4 and 5 each depend from claim 1. Because claim 1 is broader than claim 3, claim 1 is obvious over Tapolsky (or Moro) and Todd as discussed above for claim 3. *See Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1344 (Fed. Cir. 2009). The additional limitations recited in claims 4 and 5 are further obvious in view of Bullingham I.

As an initial matter, the PTO rejected these claims in view of the prior art. DFF¶139. The PTO only allowed claims 4 and 5 based on the wrong conclusion that claim 1 was patentable over the prior art. (*See* JTX-004-0341.) If an independent claim is patentable, then so are the claims that depend from it. That is as far as the PTO examined these claims. It is not surprising that BDSI did not separately argue patentability based on these parameters during prosecution. DFF¶¶139-140.

Claim 4 recites that the first buprenorphine concentration at T_{first} ("time-first") is observed at about 45 minutes. Claim 5 recites an effective buprenorphine concentration maintained for at least 4 hours. These claims recite nothing more than the inherent properties of claim 1, i.e., of buprenorphine administered from Tapolsky's BEMA device. DFF¶133. As evidenced at trial, the use of Tapolsky's BEMA device to administer buprenorphine according to claim 1 was obvious. It is axiomatic that the inherent properties from the administration of an obvious drug

delivery device are equally obvious. *See Santarus, Inc. v. Par Pharm. Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

The prior art further supports a finding of obviousness. Tapolsky's BEMA devices for any drug "yield fast onset of activity, excellent bioavailability, and sustained delivery." DFF¶28. For sublingual buprenorphine tablets, Bullingham I reports that the onset of pain relief "occurred between 15 and 45 minutes" and that a T_{first} was measured between 40 and 60 minutes. DFF¶¶42, 44. This makes sense scientifically because the drug must leave the delivery system, permeate the membranes, and absorb into the bloodstream before it can work and then reach a high enough concentration for an assay can detect it. *See* DFF¶¶116, 120, 133. Consequently, in view of Bullingham I, a POSA would have had a reasonable expectation of success of achieving a T_{first} of about 45 minutes by administering buprenorphine in Tapolsky's BEMA device. DFF¶134.

With respect to claim 5, Tapolsky further discloses that a BEMA device can maintain an effective plasma concentration of a drug for more than four hours. DFF¶29. Bullingham I also discloses that the average analgesia duration following sublingual buprenorphine administration was 534 minutes—more than double the claimed "at least 4 hours." DFF¶45. Consequently, a POSA would understand that buprenorphine can be administered using Tapolsky's BEMA device to maintain an effective concentration of "at least 4 hours." DFF¶135.

As Dr. Shafer testified, the parameters of claims 4 and 5 are not meaningful in any event. This is evidenced by the '866 patent, which does not describe these parameters as providing any particular beneficial result, much less an unexpected result, when buprenorphine is administered transmucosally according to claim 1. DFF¶136. In Table 4 of the patent, the T_{first} for buprenorphine is 45 minutes for BEMA devices that are both inside and outside the scope of the pH limitations of claim 1. DFF¶137 (JTX-001, '866 patent at 25:64-26:10). Similarly, the patent does not describe any benefit in maintaining buprenorphine concentrations effective for pain relief for at least 4 hours in contrast to shorter periods. DFF¶138.

VI. THE ASSERTED CLAIMS OF THE '539 PATENT ARE ANTICIPATED OR OBVIOUS

Claims 9 and 20 of the '539 patent recite methods of using the BEMA device of Vasisht I (i.e., the BEMA devices identically described in the '866 and '843 patents based on Tapolsky), with the added limitation that the backing layer is "buffered to a pH between about 4.0 and about 4.8." DFF¶200. Claim 20 also recites a "steady-state Cmax between about 0.156 to about 0.364 ng/mL" and that "about 1.5-8.5% of subjects experience drug related mild or moderate constipation as a TEAE." DFF¶210, DFF¶213. These claims are anticipated by Vasisht I or are obvious in view of Vasisht I alone or in further view of Reder.

A. Statement of Law

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) . "Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Id*.

The statement of law of obviousness set forth above in Section V.A with respect to the '866 and '843 patents applies to the '539 patent. Additionally, "[a] patent can be obvious in light of a single prior art reference if it would have been obvious to modify that reference to arrive at the patented invention." *Game & Tech. Co., Ltd. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1381 (Fed. Cir. 2019) . Where the "legal conclusion of obviousness is compelled on at least one asserted factual basis," i.e., a single prior art reference, a finding that "the asserted claims would have been obvious over [that single reference] as a matter of law" is appropriate. *See Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010) (affirming verdict of obviousness over a single prior art reference); *see also Realtime Data v. Iancu*, 912 F.3d 1368, 1372-73 (Fed. Cir. 2019) (affirming finding of obviousness based on a single reference where that reference "alone disclosed every element" of the claims).

B. Scope and Content of the Art

Again, BDSI raised no objection at trial that the admitted prior art "relates to the same problem as that addressed by the claimed invention," (*GPAC*, 57 F.3d at 1578 (quotation omitted)), and BDSI did not attempt to rebut the presumption that a POSA was "aware of all the pertinent prior art" admitted into evidence. *Standard Oil Co.,* 774 F.2d at 454.

1. Vasisht I (2008)

Vasisht I (DTX-017) is the publication of the PCT Application that ultimately gave rise to the '866 and '843 patents. DFF¶157. Vasisht I shares an identical specification to those patents. DFF¶157; *see* Section II.B.2 *supra*. Specifically, Vasisht I discloses the same backing layer as disclosed in and claimed by the '539 patent. DFF¶¶170-171, DFF¶¶200-203. That backing layer is also the same one used in the commercial Belbuca® devices and has a pH of 4.5, which anticipates both asserted claims. DFF¶¶204-207.

2. Reder (2001)

Reder (DTX-078) provides a transdermal delivery system for the administration of buprenorphine for the treatment of pain. DFF¶¶178-179. Reder discloses that effective pain management can be achieved using low plasma concentrations of buprenorphine, and specifically discloses a buprenorphine Cmax ("maximum concentration") of 0.185 ng/mL, which anticipates the range of asserted claim 20. DFF¶¶178-180.

C. Claim 9 is Anticipated or Obvious in View of Vasisht I

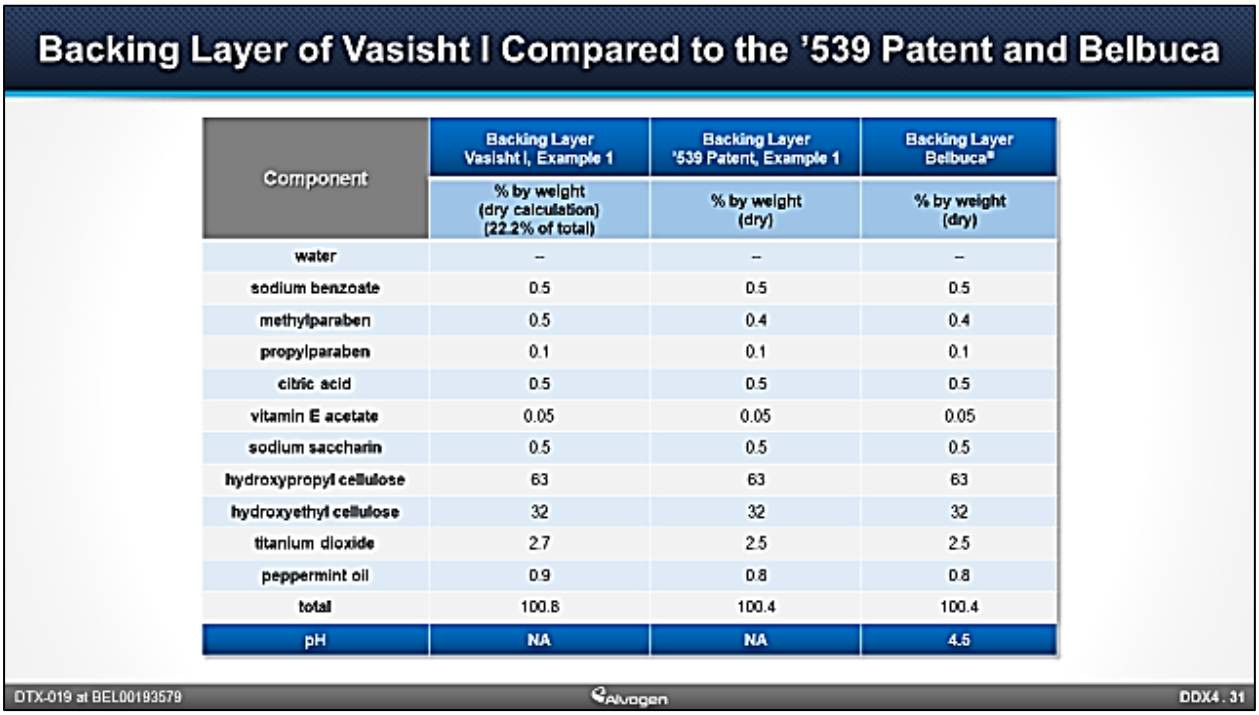
Claim 9 recites methods of treating a subject for pain using the BEMA device disclosed in Vasisht I. DFF¶¶194-200. Vasisht I discloses each limitation of claim 9 including the backing layer with the claimed pH, and it is therefore anticipated or obvious in view of Vasisht I. (Tr. 209:20-210:3; 246:23-247:5).

Although the text of Vasisht I does not recite that the backing layer has a pH "between about 4.0 and about 4.8" *in haec verba*, "inherency may supply a missing claim limitation in an obviousness analysis." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014) (collecting cases). "A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001) (citations omitted).

Vasisht I describes a method of preparing a backing layer for the claimed devices, including a recitation of the components of the backing layer used, and the wet weight percentages of each ingredient. DFF¶200. Example 1 of the '539 patent similarly recites a method of preparing a backing layer for the devices, including a recitation of the components of the backing layer used, and a dry weight percentage of each ingredient. DFF¶¶201.

Dr. Michniak-Kohn testified that comparison of the backing layer components and their weight percentages demonstrates that the backing layer of

Vasisht I is materially identical to that of the '539 patent. DFF¶¶201-202. Dr. Michniak-Kohn presented her calculations, rounded to one or two significant digits as appropriate, as shown below:



Backing Layer of Vasisht I Compared to the '539 Patent and Belbuca

Component	Backing Layer Vasisht I, Example 1	Backing Layer '539 Patent, Example 1	Backing Layer Belbuca®
	% by weight (dry calculation) (22.2% of total)	% by weight (dry)	% by weight (dry)
water	–	–	–
sodium benzoate	0.5	0.5	0.5
methylparaben	0.5	0.4	0.4
propylparaben	0.1	0.1	0.1
citric acid	0.5	0.5	0.5
vitamin E acetate	0.05	0.05	0.05
sodium saccharin	0.5	0.5	0.5
hydroxypropyl cellulose	63	63	63
hydroxyethyl cellulose	32	32	32
titanium dioxide	2.7	2.5	2.5
peppermint oil	0.9	0.8	0.8
total	100.8	100.4	100.4
pH	NA	NA	4.5

DTX-019 at BEL00193579 Alvogen DDX4.31

As Dr. Michniak-Kohn testified, the backing layer formulations of Vasisht I and the '539 patent slightly differ with respect to peppermint oil (flavoring agent) and titanium dioxide (coloring agent), but the slight differences would not impact the pH of the layer. DFF¶202, DDX4.31. Consequently, the backing layers of Vasisht I and of the '539 patent necessarily have the same pH. DFF¶¶203, 207. It follows, therefore, that the pH of the backing layer claimed by the '539 patent is inherently disclosed by Vasisht I. DFF¶203.

The pH of the backing layer in Belbuca® corroborates this conclusion. Belbuca® is the commercial embodiment of Vasisht I (i.e., the '866 patent) and at least claim 9 the '539 patent. D.I. 245, 246. Dr. Michniak-Kohn testified that BDSI's own documents confirm that the backing layer of Belbuca®, formulations F14 and F24, is materially identical to Vasisht I and the '539 patent. DFF¶¶205-206, DDX4.31. BDSI's corporate witness, Joey Thomas, testified that the Belbuca® backing layer has a pH of 4.5. DDF¶204.

Accordingly, Vasisht I anticipates or renders obvious claim 9 and, as discussed below, renders claim 20 obvious in view of Reder.[21] This did not escape the eye of the Examiner. *See* DFF¶208. Once again, however, BDSI resorted to deception and submitted false information to the PTO by way of a sworn declaration from Dr. Vasisht. DFF¶208. In his declaration, Dr. Vasisht stated that he replicated the backing layer of Vasisht I and found its pH to be (on average) 5.61. DFF¶208. Dr. Vasisht never told the PTO that the identical backing layer formulation, reported to the FDA as part of the Belbuca® NDA, had a pH of 4.5.

[21] Alvogen has presented evidence that Vasisht I teaches every limitation of claim 9. DFF¶¶194-209. At trial, Dr. Michniak-Kohn opined that claim 9 is "obvious over Vashist [*sic,* Vasisht I]." (Tr. at 246:23-247:5). As the Federal Circuit has explained, "anticipation is the epitome of obviousness." *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019), quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) . To the extent the Court finds that the evidence does not establish anticipation, it certainly demonstrates that claim 9 is obvious in view Vasisht I.

DFF¶¶204, 208. Consequently, Dr. Vasisht either falsified or omitted material data. *See* DFF¶208. Either way, BDSI never attempted to provide a plausible explanation at trial.

However, BDSI attempted to argue at trial that the pH range of the backing layer provided surprising and unexpected results. For example, Dr. Taft testified about BDSI testing of different backing layer formulations (identified as "F1," "F2," "M1," and "M2") that either included or did not include citric acid. DFF¶228. Dr. Taft opined that the inclusion of citric acid resulted in unexpectedly improved bioavailiabity of buprenorphine. (Tr. 803:22-806:19). Dr. Taft's opinion is inapposite inasmuch as it ignores the fact that Vasisht I teaches a backing layer that includes citric acid (*see* DFF¶171) and has a pH within the claimed range. DFF¶229, *see also* DFF¶207. In other words, any evidence of unexpected results pertaining to citric acid and the pH of the backing layer would be attributable to Vasisht I, not the asserted claims. DFF¶231.

D. Claim 20 is Obvious in View of Vasisht I and Reder

Claims 20 (which incorporates claim 1) recites similar methods as those recited in claim 9 for treating a subject for pain using the BEMA device disclosed in Vasisht I. DFF¶¶194-199. BDSI does not dispute that Vasisht I discloses the limitations of claims 20, except (1) the pH of the backing layer "between about 4.0 and about 4.8," (2) the steady-state Cmax range of "about 0.156 to about 0.364

ng/mL," and (3) the population of patients that experience constipation (i.e., "between about 1.5-8.5% of subjects").[22] The backing layer pH in claim 20 is identical to that of claim 9, and is anticipated and/or obvious in view of Vasisht I for the reasons already stated. For the reasons set forth below, claim 20 is obvious in view of Vasisht I and Reder. (Tr. 246:23-247:9.)

1. Vasisht I Teaches the Constipation Incidence of Claim 20

The method of claim 20 further requires that "about 1.5-8.5% of subjects experience drug related mild or moderate constipation as a [treatment emergent adverse event] TEAE." DFF¶210. During prosecution, BDSI never attempted to support the patentability of this claim independent of claim 1—the claims would rise or fall together. DFF¶210. This is not surprising inasmuch as the claim merely recites the results of using the BEMA devices disclosed by Vasisht I. *See* DFF¶211. Only one strength of Alvogen's ANDA products infringes claim 20, specifically the 150 mcg strength. D.I. 245, 246. This strength is among those dosages recited in Vasisht I. *See* DFF¶167.

Vasisht I discloses that subjects using buprenorphine BEMA devices experience "little or no constipation." DFF¶211. The claimed range is consistent with the expectation of a POSA that 5-10% of patients on chronic opioid therapy

[22] As noted above with respect to claim 9, the remaining uncontested limitations of claim 20 are taught by Vasisht I. Section VI.C *supra*, DFF¶¶194-199.

experience constipation as a side effect. DFF¶212. As Dr. Fine testified, constipation is a side effect that results from the drug and dosage amount, not the drug delivery system. DFF¶212. For example, the package insert for Temgesic® sublingual buprenorphine tablets, published in 2008, states that treatment with the buprenorphine tablets resulted in less than 1% of patients treated experiencing constipation as an adverse event. DFF¶211.

2. Vasisht I and Reder Disclose the Steady-State Cmax of Claim 20

Claim 20 requires "a steady-state Cmax of plasma buprenorphine concentration in a range between about 0.156 and about 0.364 ng/mL." DFF¶213. Dr. Shafer explained that Cmax refers to "the maximum plasma concentration of a drug following administration" and that it "depends on the drug, on the device, and on the dose." DFF¶214. Steady-state Cmax refers to the Cmax observed upon administration of repeated doses, and thus further "depends on the dosing interval." DFF¶214. Consequently, steady-state Cmax is a pharmacokinetic parameter that is depends on a given dose of drug from a given device, over a given dosing interval. DFF¶214.

Vasisht I discloses buprenorphine, the claimed BEMA device, the claimed dosage range, and the dosing interval. DFF¶215; *see* Sections VI.B.1; VI.C *supra*. Vasisht I teaches that buprenorphine is dose proportional, such that the Cmax observed scales linearly with the dose of buprenorphine administered. DFF¶168.

Vasisht I further teaches a wide range of doses of buprenorphine that may be included in the device, some of which are too high to achieve these steady-state Cmax values.[23] DFF¶¶167, 216. However, a POSA would readily have been able to select doses of buprenorphine, as taught by Vasisht I, for use in the device of Vasisht I to provide a steady-state Cmax within the claimed range. DFF¶223.

Furthermore, Reder supplies a steady-state buprenorphine Cmax of about 0.185 ng/mL that is effective to treat pain. DFF¶¶179, 215. A Cmax of 0.185 ng/mL anticipates the claimed range of "between about 0.156 and about 0.364 ng/mL." DFF¶¶180, 215.

A POSA would have been motivated to combine the teachings of Vasisht I and Reder because both references teach the effective administration of buprenorphine to treat or manage pain. DFF¶218. A POSA would understand Vasisht I's BEMA device could be routinely configured (for example, by adjusting the dose) in order to provide the Cmax taught by Reder that effectively treats chronic pain. DFF¶¶217, 223. A POSA would have reasonably expected success

[23] Before trial, the parties stipulated that Alvogen's proposed 75, 300, 450, 600, 750 and 900-mcg doses do not satisfy the steady-state Cmax limitations and, therefore, do not infringe the claim, but that Alvogen's proposed 150-mcg dose would infringe. D.I. 245, 246.

in achieving a steady-state Cmax in the claimed range as taught by Reder using the Vasisht I BEMA devices.[24] DFF¶¶215-223.

At trial, BDSI attempted to argue that a POSA would not consult Reder based on its disclosure of a transdermal device. (Tr. 830:5-832:22). However, Reder explicitly states that "[a]ny mode of [administration] may be utilized" to obtain the desired plasma concentrations of buprenorphine, including, "[f]or example" that "the buprenorphine may be administered transdermally, parenterally, sublingually, orally, buccally, rectally, etc." DDF¶¶181-189, 220-222. Moreover, a POSA would have understood that the critical disclosure in Reder is a buprenorphine Cmax that is effective to treat pain, not the route of administration. DFF¶219. As Dr. Shafer's unrebutted testimony explains, how the buprenorphine gets into the blood of the treated subject is not relevant because once there, it treats pain. DFF¶¶221.

[24] Other prior art would have guided a POSA in this respect. Bullingham I and Bullingham II disclose Cmax data resulting from 400-mcg and 800-mcg doses of sublingual buprenorphine tablets. DFF¶¶184-186, 188-189, 224. These doses resulted in Cmax values above the Cmax range in claim 20. DFF¶224. However, using this information, a POSA would have calculated a "per mcg" Cmax for buprenorphine and a steady-state Cmax for a given dose (i.e., about 100-250 mcg) selected from the range disclosed in Vasisht I. DFF¶¶224-226; DDX3.66.

VII. BDSI'S PROSECUTION CONDUCT OBSTRUCTED A FULL AND FAIR EXAMINATION

The United States Supreme Court has stated that "if the PTO did not have all material facts before it, its considered judgment may lose significant force," and the "challenger's burden to persuade the [factfinder] of its invalidity defense by clear and convincing evidence may be easier to sustain." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 111 (2011). BDSI's conduct before the PTO goes far beyond the incomplete record that the Supreme Court addressed in *i4i* where the presumption loses its force. *See id.*

As evidenced at trial and noted throughout this brief, BDSI repeatedly made materially false statements and presented materially false data to the PTO in order to obtain the three patents-in-suit. Specifically, BDSI mischaracterized the teachings of Tapolsky (DFF¶141), omitted the pH of Suboxone® and said that it was unbuffered (DFF¶146), provided false pH values for two key samples (BEMA 1 and BEMA2) (DFF¶147), provided false pH data for the Vasisht I backing layer, and omitted the pH of the Belbuca® backing layer (DFF¶208). In view of these repeated misrepresentations and omissions, BDSI manifestly intended the PTO to issue the patents-in-suit based on false pretenses. BDSI's inexcusable conduct irreparably damaged the statutory presumption of validity that the patents-in-suit otherwise would have.

Courts including the Third Circuit have thrown out the presumption of validity when the patentee misleads the PTO. *See, e.g., Tenneco Chems., Inc. v. William T. Burnett & Co.*, 691 F.2d 658, 665-68 (4th Cir. 1982) ("By misleading the Patent Office, plaintiff destroys the presumption of validity which would have attended the patent."); *Metallurgical Exoproducts Corp. v. Pittsburgh Metals Purifying Co.*, 393 F. Supp. 1104, 1107 (W.D. Pa. 1975), aff'd, 532 F.2d 747 (3rd Cir. 1976) ("The law is clear that no presumption of validity will be awarded to a patent where there is evidence that the Patent Office has been misled as to the true import of prior art references"); *Kahn v. Dynamics Corp. of Am.*, 508 F.2d 939, 942 (2nd Cir. 1974) (same); *John Deere Co. v. Graham*, 333 F.2d 529, 530 (8th Cir. 1964) (same). These courts do not say that evidence of misleading the PTO rebuts the presumption; rather that such evidence destroys it.

Although these cases predate the *i4i* decision, they each stand on sound and basic legal principles that the statutory presumption of validity evaporates in view of evidence that the patentee made materially false statements to the PTO, irrespective of any pleading or finding of inequitable conduct. *See Tenneco*, 691 F.2d at 665-68; *Metallurgical*, 393 F. Supp. at 1107; *Kahn*, 508 F.2d at 942; *John Deere*, 333 F.3d at 529. Without the benefit of the presumption, the law should be that BDSI carries the burden of persuasion on validity (*see* FED.R.EVID. 301) , which it has not done in view of the trial record and prior art evidence.

VIII. THERE WAS NO LONG-FELT NEED

At trial, BDSI contended that there was a long-felt need for buprenorphine products approved by FDA to treat pain in view of the opioid epidemic because buprenorphine allegedly had improved safety and lower abuse potential. However, the inventors did not intend to address the opioid crisis or any other alleged problem now cited by BDSI. The patents-in-suit do not mention the long-felt need. The FDA did not accelerate the approval of Belbuca® based on a long-felt need. Rather, the inventors were simply interested in expeditiously developing a BEMA product for their fledgling company based on the Tapolsky platform.

A. Statement of Law

A patentee may attempt to rebut obviousness through evidence of secondary considerations of non-obviousness. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007). "[A] patentee bears the burden of production with respect to evidence of secondary considerations." *ZUP, LLC v. Nash Mfg. Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018) . A long felt need arises when there is "an articulated identified problem and evidence of efforts to solve that problem." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d. 1324, 1332-33 (Fed. Cir. 2009)) (quoting *Tex. Instruments v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993)). Where, as here, the differences between the claimed invention and the prior art are "minor," evidence of secondary considerations is not sufficient to support the

validity of a claim. *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996).[25]

B. BDSI Relies on Evidence That Lacks a Nexus with the Claimed Drug Delivery Devices

Absent a nexus, BDSI's allegation of a long-felt need does not rebut the obviousness of the asserted claims. *In re Karpf*, 758 Fed.Appx. 960, 965 (Fed. Cir. 2019) . BDSI is entitled to a rebuttable presumption of nexus only if it ties the evidence specifically to "the invention disclosed and claimed." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019)) (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988))).

BDSI proffered Dr. Richard Rauck, a paid member of its Speakers Bureau, who testified that there was a need in 2006 for an opioid with reduced side effects, specifically reduced respiratory depression and overdose risk. (Tr. 874:14-23) Dr. Rauck's testimony is inapposite inasmuch as none of the asserted claims mentions addiction, respiratory depression, or QT prolongation. DFF¶235. Further, Belbuca®'s properties with respect to these risks are dependent upon the buprenorphine molecule itself, not the specific drug delivery devices claimed or the Belbuca® product. *See Fox Factory*, 944 F.3d at 1373; DFF¶236.

[25] See D.I 230, Ex.5A at ¶¶ 146-157 for further law regarding long-felt need.

Dr. Rauck also emphasizes that Belbuca® is currently a schedule III opioid for the treatment of pain (*see, e.g.*, Tr. 874:24-875:12). Dr. Rauck's testimony is devoid of any nexus because it depends upon the DEA's current scheduling of buprenorphine not the asserted claims. DFF¶235.[26] Furthermore, Dr. Rauck's testimony again relates to the buprenorphine molecule already known to treat chronic pain and not to the allegedly novel aspects of the BEMA devices that deliver it. *See Fox Factory*, 944 F.3d at 1373; *see also S. Alabama Med. Sci. Found. v. Gnosis S.P.A.*, 808 F.3d 823, 827 (Fed. Cir. 2015) (affirming a finding of no nexus where the patent owner "failed to connect the evidence of industry praise to the novel elements of the claims," given that "the praise was particularly directed to . . . an element already known in the prior art").

Dr. Rauck further opined that Belbuca® satisfies a long-felt need for a safer alternative for treating patients with chronic pain. (Tr. 897:13-898:7.) Dr. Rauck's principle cited reason is the risk of addiction and misuse of opioids, i.e., the "opioid crisis." (*See e.g.*, Tr. 864:21-867:6.) Without question, the opioid crisis is a problem. However, by 2006, the opioid crisis was at most an emerging problem that those in the field did not concretely recognize for several more years.

[26] The DEA can, and does, reclassify opioids as circumstances change. DFF¶237. In fact, the DEA has already changed buprenorphine's scheduling once, from a Schedule II opioid to a Schedule III opioid, and this is why Belbuca® is currently Schedule III. The DEA made the change in 2002, years before the patents-in-suit or Belbuca® even existed. DFF¶238.

Dr. Rauck testified that the problems that led to the opioid crisis might have begun as early as the 1990s (Tr. 865:6-865:14). Nevertheless, he did not take issue with Dr. Fine's testimony that those in the field only began becoming concerned in the early to mid-2000s. DFF¶239. The trial evidence corroborates Dr. Fine's testimony. For example, the earliest documentary evidence in the trial record of the "crisis" is dated 2009. DFF¶240. And there is no evidence that the opioid crisis was an articulated problem that others had made efforts to solve as of 2006, the earliest filing date of the patents-in-suit. *See Perfect Web Techs.,* 587 F.3d. at 1332-33.

Finally, nothing in the record establishes that Belbuca® even addressed the opioid crisis. Dr. Rauck himself concedes that the opioid crisis is ongoing. DFF¶241.

C. The Belbuca® Label Confirms That Belbuca® Is Not Safer Than Other Products

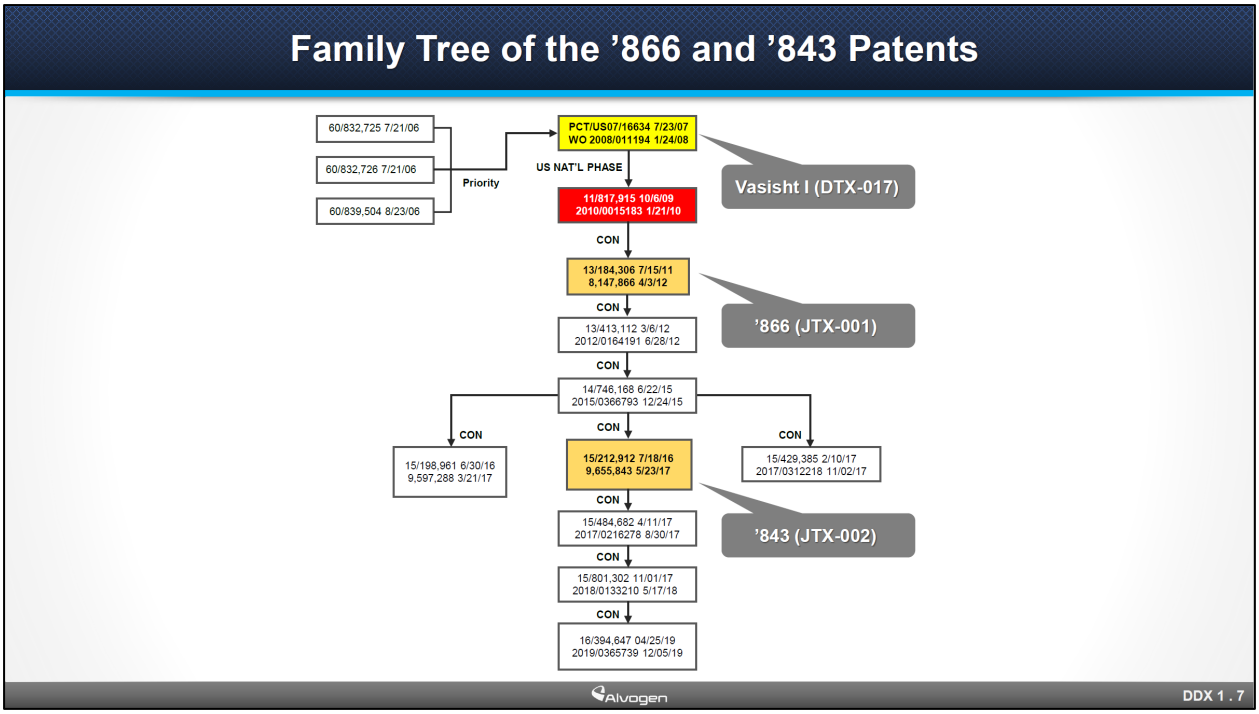
BDSI points to various patient safety issues associated with opioids as problems allegedly "solved" by Belbuca®. However, FDA requires the Belbuca® product label to include a "black box warning" about these very same safety issues. DFF¶242. The Belbuca® label is unsurprisingly similar to the label for other buprenorphine products, such as Butrans®, a transdermal buprenorphine product approved several years before Belbuca®. DFF¶¶249-253. That is because the

safety risks are characteristics of buprenorphine itself, and do not depend on how the drug is administered. DFF¶236.

Furthermore, the Belbuca® label warns of risks associated with most other opioids, such as (1) "risks of addiction, abuse, and misuse, which can lead to overdose and death," DFF¶243; (2) "Misuse or abuse of BELBUCA® by chewing, swallowing, snorting or injecting buprenorphine," DFF¶244; (3) "Serious, life-threatening, or fatal respiratory depression," DFF¶245; (4) "Risk of Prolonged QTc Interval," DFF¶¶246-247; and (5) "nausea, constipation, headache, vomiting, dizziness, and somnolence," DFF¶248. Consequently, the label squarely contradicts BDSI's argument that Belbuca® satisified a long-felt need for a safer opioid product.

IX. CLAIMS 3, 4, 5, AND 10 OF THE '866 AND CLAIMS 8 AND 20 OF THE '843 PATENT ARE ANTICIPATED

The family tree of the '866 and '843 patents is set forth below:



As shown in the family tree, Vasisht I (yellow) published January 2008. DFF¶156. In order to remove Vasisht I as prior art, claims 3, 4, 5, and 10 of the '866 patent and claims 8 and 20 of the '843 patent must be entitled to the July 2007 filing date of the '915 application (red) (DTX-206). If, as Alvogen contends, the patents cannot claim priority to the '915 application, then there is no real dispute that these claims are invalid as anticipated by Vasisht I.

A. Statement of Law

"A person shall be entitled to a patent unless . . . the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b) (2012). In order for BDSI to claim priority to Vasisht I, 35 U.S.C. § 120 requires that Vasisht I includes a disclosure that meets the requirements of 35

U.S.C. § 112, first paragraph. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997); *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002).[27]

Because Vasisht I discloses a broad pH range of 4-7.5, but does not disclose the specific pH ranges claimed in the '866 and '843 patents, i.e., 4-6, 4.5-5.5, 4.5-5, the asserted patent claims added new matter unsupported by Vasisht I. *See In re Wertheim*, 541 F.2d 257, 262-64 (C.C.P.A. 1976) (finding claimed range of "at least 35%" in child application was unsupported by parent and Swiss applications that disclosed a range of "25-60%"); *Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995) (finding that claims requiring an alloy "with nickel constituting about 50 to about 60% of the alloy" were not supported by grandparent application that "only disclosed a nickel range of 45-55%").

B. The '915 Application Does Not Support BDSI's Priority Claim

The priority date analysis turns on a POSA's interpretation of paragraph [0063] of the '915 application.

[27] See D.I. 230, Ex.5A at ¶¶85-90 for further law regarding priority and ¶¶93-107 regarding anticipation.

> **[0063]** In one embodiment, e.g., when the medicament is buprenorphine, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 4.0 and about 7.5. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 6.0. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 5.5 to about 6.5, or between about 6.0 and 6.5. In yet another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and 7.5, or between about 7.25 and 7.5. In other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

(DTX-206-0011). This paragraph discloses the pH for embodiments where buprenorphine is the drug in the BEMA device, and refers to the device as a whole not only the mucoadhesive polymeric diffusion environment. More specifically, this paragraph discloses the following values and ranges for the pH of the mucoadhesive polymeric diffusion environment: (a) between about 4.0 and about 7.5; (b) about 6.0; (c) about 5.5 to about 6.5; (d) between about 6.0 and 6.5; (e) about 7.25; (f) between about 7.0 and 7.5; and (d) between about 7.25 and 7.5. DFF¶269.

Dr. Michniak-Kohn testified that these pH values and ranges in paragraph [0063], nearly all of which extend above a pH of 6, are uniformly higher than the claimed ranges. This difference is significant because, at the time BDSI filed the

applications, it only had data for BEMA 1 ("pH 7.25") and BEMA 2 ("pH 6").[28] DFF¶269. The uniformly higher values and ranges in [paragraph 0063] and the BEMA 1-2 devices would not enable a POSA to "immediately discern" that the inventors were in possession of the narrower and much lower claim ranges. *See Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000) (to satisfy the written description requirement "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims").

BDSI appears to concede that the disclosed pH values and ranges disclosed in paragraph [0063] do not enable the claimed pH ranges. Instead, BDSI focuses on the catch-all sentence of paragraph [0063], which states "[i]n other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0 or 7.5, or any incremental value thereof." (*See* Tr. 656:24-657:10.)

Dr. Michniak-Kohn testified that a POSA would have understood this sentence to mean what it says in that it refers to the pH of the device as whole, not the pH of the polymeric diffusion layer of the device. DFF¶270. The asserted claims sufficiently corroborate her testimony inasmuch as both terms appear in a manner where the "device" includes a "polymeric diffusion environment" amongst

[28] The Finn Declaration suggests that inventors did not settle upon the range of 4-6 until years after the '915 application was filed.

other things, such as a backing layer. The specification of the '915 application also corroborates her testimony inasmuch as it uniformly and repeatedly uses the term "device" in reference to the dosage form itself that is distinct from the "polymeric diffusion environment" which is separately defined and comprises but one element of "the device." DFF¶271.

Dr. Williams points to paragraph [0020] and the Abstract of the '726 provisional application, to which the '915 application claims priority, as enabling the narrower claimed pH ranges. (Tr. 660:9-661:3.) However, the disclosure of the '726 provisional application is entirely consistent with that of the '915 application. For example, the Abstract states that the pH of the mucoadhesive layer is between about 4 and about 7.5 and paragraph [0020] only mentions the pH of "the device". DFF¶272.

Accordingly, claims 3, 4, 5, and 10 of the '866 patent and claims 8 and 20 of the '843 patent are not entitled to the filing date of the '915 application. As such, these claims are invalid as anticipated by Vasisht I. *See* DFF¶¶273-275.

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Dated: March 30, 2021

CERTIFICATE OF COMPLIANCE

I hereby certify that the text of the foregoing document uses a 14-point Times New Roman typeface and contains 12,414 words as determined by the word count feature of Microsoft Word (excluding the caption, tables, signature block, and certifications).

Date: March 30, 2021

/s/ Steven H. Sklar
Steven H. Sklar